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(71)Applicant : NIPPON SHINYAKU CO LTD
(72)Inventor : MIYAWAKI SHIGEKI
TAKESO ERI
TSUJIMOTO GOZO

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(54) NEW ANIMAL DEVELOPING PATHOLOGIC SYMPTOM

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a mouse developing a pathologic symptom similar to human IgA nephropathy.
SOLUTION: A mouse quickly developing the pathologic symptom of IgA nephropathy at a high rate is prepared from ddY-strain mouse commercially available as a closed colony animal by carrying out the selective breeding

for achieving quick onset of IgA nephropathy and high onset rate using serum IgA level as an index. The mouse developing the pathologic symptom is extremely useful as a model animal for the investigation of the pathologic symptom of human IgA nephropathy because the mouse shows high blood IgA level from young state and exhibits high deposition of IgA to the glomerulus with age and the resulting development of glomerulosclerosis caused by the proliferation of mesangial cell and the growth of mesangial substrate. The participation of various growth factors are recognizable during the onset process and, accordingly, the animal is extremely useful also as a drug efficacy evaluation model for the development of a drug targeting these factors.

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CLAIMS

[Claim(s)]
[Claim 1] The symptoms manifestation mouse which has either or both among the following 1 and the description of 2 by 5-10 weeks old.
1) The amount of platelet derived growth factor (PDGF) gene expression is 1.2 to 1.5 times the ddY system mouse.
2) The amount of manifestations of the inner-bark differentiation gene -5 (edg-5) is 1.5 to 3.6 times the ddY system mouse.
[Claim 2] The genotype of Idh1 locus is an a mold and the genotype of Pep3 locus is a b mold. The genotype of Akp1 locus is a b mold and the genotype of Hc locus is an o mold. The genotype of Car2 locus is an a mold and the genotype of Mup1 locus is an a mold. The genotype of Gpd1 locus is a b mold and the genotype of Pgm1 locus is an a mold. The genotype of Ldr1 locus is an a mold and the genotype of Gpi1 locus is an a mold. The genotype of a Hbb locus is an s mold and the genotype of Es1 locus is a b mold. The genotype of Es2 locus is a b mold and the genotype of Thy1 locus is a b mold. The genotype of Mod1 locus is an a mold and the genotype of a Trf locus is a b mold. The genotype of Es3 locus is a c mold and the genotype of H2K locus is an s mold. The genotypes of H2D locus are b mold, d mold, k mold, q mold, and a mold applicable to neither of s mold. The genotype of Ly2 locus is a b mold and the genotype of Ly3 locus is a b mold. The genotype of a Hba locus is a c mold and the genotype of an IghC locus is an a mold. The genotype of Np1 locus is an a mold and the genotype of Es10 locus is a b mold. The genotype of C3 locus is a b mold and the genotype of Glo1 locus is an a mold. The genotype of Ly1 locus is a b mold. D1Mit43 locus, D1Mit48 locus, D1Mit70 locus, D1Mit76 locus, D1Mit132 locus, D1Mit215 locus, D2Mit79 locus, D2Mit98 locus, D2Mit113 locus, D3Mit105 locus, D3Mit117 locus, D3Mit152 locus, D4Mit89 locus, D4Mit103 locus, D4Mit146 locus, D4Mit209 locus, D5Mit20 locus, D5Mit99 locus, D5Mit136 locus, D6Mit113 locus, D6Mit170 locus, D7Mit46 locus, D7Mit57 locus, D7Mit80 locus,

D7Mit131 locus, D8Mit58 locus, D8Mit64 locus, D8Mit87 locus, D9Mit35 locus, D9Mit66 locus, D9Mit120 locus, D10Mit84 locus, D10Mit102 locus, D11Mit74 locus, D11Mit164 locus, D11Mit174 locus, D11Mit184 locus, D11Mit202 locus, D12Mit80 locus, D12Mit116 locus, D12Mit126 locus, D13Mit1 locus, D13Mit13 locus, D13Mit117 locus, D14Mit48 locus, D14Mit83 locus, D14Mit94 locus, D14Mit111 locus, D15Mit42 locus, D15Mit83 locus, D16Mit34 locus, D17Mit24 locus, D17Mit113 locus, D17Mit150 locus, D18Mit40 locus, D18Mit92 locus, D19Mit6 locus, D19Mit56 locus, The symptoms manifestation mouse whose genotype of D19Mit61 locus, DXMit73 locus, DXMit79 locus, and DXMit98 locus is different genotype from a BALB/c system mouse.

[Claim 3] The genotype of Idh1 locus is an a mold and the genotype of Pep3 locus is a b mold. The genotype of Akp1 locus is a b mold and the genotype of Hc locus is an o mold. The genotype of Car2 locus is an a mold and the genotype of Mup1 locus is an a mold. The genotype of Gpd1 locus is a b mold and the genotype of Pgm1 locus is an a mold. The genotype of Ldr1 locus is an a mold and the genotype of Gpi1 locus is an a mold. The genotype of a Hbb locus is an s mold and the genotype of Es1 locus is a b mold. The genotype of Es2 locus is a b mold and the genotype of Thy1 locus is a b mold. The genotype of Mod1 locus is an a mold and the genotype of a Trf locus is a b mold. The genotype of Es3 locus is a c mold and the genotype of H2K locus is an s mold. The genotypes of H2D locus are b mold, d mold, k mold, q mold, and a mold applicable to neither of s mold. The genotype of Ly2 locus is a b mold and the genotype of Ly3 locus is a b mold. The genotype of a Hba locus is a c mold and the genotype of an IghC locus is an a mold. The genotype of Np1 locus is an a mold and the genotype of Es10 locus is a b mold. The genotype of C3 locus is a b mold and the genotype of Glo1 locus is an a mold. The genotype of Ly1 locus is a b mold. D1Mit43 locus, D1Mit48 locus, D1Mit70 locus, D1Mit76 locus, D1Mit132 locus, D1Mit215 locus, D2Mit79 locus, D2Mit98 locus, D2Mit113 locus, D3Mit105 locus, D3Mit117 locus, D3Mit152 locus, D4Mit89 locus, D4Mit103 locus, D4Mit146 locus, D4Mit209 locus, D5Mit20 locus, D5Mit99 locus, D5Mit136 locus, D6Mit113 locus, D6Mit170 locus, D7Mit46 locus, D7Mit57 locus, D7Mit80 locus, D7Mit131 locus, D8Mit58 locus, D8Mit64 locus, D8Mit87 locus, D9Mit35 locus, D9Mit66 locus, D9Mit120 locus, D10Mit84 locus, D10Mit102 locus, D11Mit74 locus, D11Mit164 locus, D11Mit174 locus, D11Mit184 locus, D11Mit202 locus, D12Mit80 locus, D12Mit116 locus, D12Mit126 locus, D13Mit1 locus, D13Mit13 locus, D13Mit117 locus, D14Mit48 locus, D14Mit83 locus, D14Mit94 locus, D14Mit111 locus, D15Mit42 locus, D15Mit83 locus, D16Mit34 locus, D17Mit24 locus, D17Mit113 locus, D17Mit150 locus, D18Mit40 locus, D18Mit92 locus, D19Mit6 locus, D19Mit56 locus, The genotype of D19Mit61 locus, DXMit73 locus, DXMit79 locus, and DXMit98

locus is different genotype from a BALB/c system mouse. By 5-10 weeks old The symptoms manifestation mouse according to claim 1 or 2 which has either or both among the following 1 and the description of 2.
1) The amount of PDGF gene expression is 1.2 to 1.5 times the ddY system mouse.
2) The amount of edg-5 gene expression is 1.5 to 3.6 times the ddY system mouse.
[Claim 4] The symptoms manifestation mouse according to claim 1 to 3 whose symptoms to discover are human immunoglobulin A (IgA) nephropathy Mr. symptoms.
[Claim 5] The symptoms manifestation mouse according to claim 4 whose IgA glomerulonephritis Mr. symptoms are mesangium sclerosis.
[Claim 6] The symptoms manifestation mouse according to claim 5 which discovers mesangium sclerosis with age for four months.
[Claim 7] The symptoms manifestation mouse with which the Ministry of International Trade and Industry National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology patent microorganism deposition pin center,large was entrusted with the fertilized egg as trust number FERM P-18150 No.
[Claim 8] The screening procedure of the glomerulosclerosis progress inhibitor characterized by using a symptoms manifestation mouse according to claim 1 to 7 as an individual, or an extracellular-matrix production inhibitor.
[Claim 9] The screening procedure of the glomerulosclerosis progress inhibitor characterized by using the organization or cell originating in a symptoms manifestation mouse according to claim 1 to 7, or an extracellular-matrix production inhibitor.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to a Homo sapiens IgA glomerulonephritis Mr. symptoms manifestation mouse.
[0002] This invention is used in the area of research of medicine or pharmaceutical sciences for a break through of the symptoms manifestation device of human IgA glomerulonephritis, research of a cure, or development of a remedy.
[0003]
[Description of the Prior Art] IgA glomerulonephritis occupies about 30% of the chronic glomerulonephritis of our country, moreover it is said that it goes on the 10 to 20% to the terminal renal failure which needs dialysis treatment, and the onset of this symptom, and a break through of a progress mechanism and research of a cure are pressing need. In such a research field, it has been anxious for existence of the suitable model animal which discovers the symptoms concerned.
[0004] Since several sorts of experimental IgA glomerulonephritis models [each] (Kidney International 31:1-7 (1987)) developed until now have a field unnatural in origin theory, it cannot be said that the symptoms of human IgA glomerulonephritis are not necessarily reflected in accuracy.
[0005] As a model which carries out the natural onset of the IgA glomerulonephritis, only the ddY system mouse marketed as a mouse of a closed colony is known (Kidney International 27:756-761 (1985)).
[0006] However, the incidence rate of the IgA glomerulonephritis Mr. symptoms in a ddY system mouse of it being low and moreover advanced IgA deposition coming to be accepted to be about 20% in mesangium is as late as 14-month age or subsequent ones. Furthermore, since the ddY system which is the mouse of a closed colony is dissymmetry 1 hereditarily, it is difficult to use for a break through of a symptoms manifestation device to the analysis

of a disease gene of cause not to mention a completely unsuitable thing. As described above, in the ddY system mouse known as an only model which carries out the natural onset of the IgA glomerulonephritis Mr. symptoms, economical effectiveness in case time course until it results in a symptoms manifestation in the top where the rate of the onset is low uses for research by making this into a symptoms model from a ******** extremely is very low. Furthermore, since the factor which participates in the symptoms manifestation in a ddY system mouse is unknown, the activity as a drug effect valuation modeling in the innovative drug development which clarified the operation target of a drug is not borne.

[0007] A ddY system mouse is the animal of a closed colony, and that the incidence rate of the IgA glomerulonephritis Mr. symptoms in a ddY system mouse is only 20% is also the cause by which it is thought that it is because it is not fixing hereditarily, and this makes hereditary analysis of an onset factor difficult.

[0008]

[Problem(s) to be Solved by the Invention] This invention aims at showing the symptoms of IgA glomerulonephritis Mr. symptoms in an early stage and high rate, and developing a symptoms model mouse with the clear onset factor.

[0009]

[Means for Solving the Problem] this invention persons carried out the breeding by selection which hung up for the purpose of the early onset and the high onset of IgA glomerulonephritis, and made the blood serum IgA value the index by being made from the ddY system mouse marketed as an animal of a closed colony, and succeeded in making the animal (this invention mouse) which discovers the symptoms concerned to an early stage and high rate. Since the symptoms manifestation mouse (henceforth the "this invention mouse") concerning this invention shows the high price in [IgA] blood from the time of juvenile and presents growth of the advanced deposition of IgA to mesangium, and the mesangial cell accompanying it, and progress of the glomerulosclerosis by the hyperplasia of a mesangium substrate with aging, it is very useful as a model animal for symptoms research of Homo sapiens IgA glomerulonephritis. Moreover, since the intervention of various growth factors is accepted in the onset process, it is very useful also as a drug effect valuation modeling in the drugs development which used those factors as the target.

[0010] As a result of analyzing the kidney pathology organization image of this invention mouse, the manifestation [high rate / as a different new description from the conventional ddY system mouse / glomerulosclerosis lesion] was accepted. Then, it succeeded in raising the system which fixed thoroughly the characteristic which this invention mouse has by repeating

the sib mating of 40 or more generations by making the early onset of high IgA **** and mesangium sclerosis into an index. Furthermore, research on the symptoms manifestation device in this invention animal was able to be advanced, the new description with which it is not known by the conventional ddY system mouse, or the conventional ddY system mouse was not equipped was able to be discovered so that it might state in detail later, and this invention mouse was able to be established as a new valuation modeling in the cure for Homo sapiens IgA glomerulonephritis thru/or development of a remedy.

[0011] It was able to succeed in the early onset, training and inbreeding-izing of the system which fills both the objects of a high incidence rate, and a break through of the onset factor by the gene analysis in this way, and this invention was able to be completed.

[0012] In this invention, the DNA fragment with which a locus is used as a gene or a marker on a chromosome says the location which at least fortune-telling does, and genotype means the presentation (mold) of the gene or DNA fragment of the couple to which at least fortune-telling does each locus. All loci are being fixed to the gay in this invention mouse.

[0013] In this invention, the deposition to the mesangium of IgA, IgG, and complement, the high IgA value in blood, etc. call the symptoms generally seen in human IgA glomerulonephritis, and the same symptoms IgA glomerulonephritis Mr. symptoms, and it is divided roughly into the active acute lesion accompanied by a sharp fecundity change of demilune formation etc., and the chronic glomerulosclerosis lesion by mesangium substrate protein hyperplasia.

[0014] In this invention, an extracellular-matrix production inhibitor means the matter which controls the extracellular-matrix production leading to organization fibrosis, for example, par phenidone and tranilast are mentioned.

[0015] In this invention, a glomerulosclerosis progress inhibitor means the matter with the operation which controls the hyperplasia of the mesangium substrate protein in mesangium, and the progress of the glomerulosclerosis which therefore takes place calmly, for example, an anti-TGF-beta antibody and decorin are mentioned.

[0016]

[Embodiment of the Invention] Hereafter, this invention mouse is explained in full detail. this invention mouse is acquirable with the following procedures.

[0017] this invention persons purchased 52 females and 52 males of a ddY system which are first marketed from Japan SLC, Inc. as a mouse of a closed colony, and measured age and the blood serum IgA value in four-month age by the ELISA method (Klein-Schneegans A.S.et al., J.Immunol.Methods, 1989; 119:117-125) for those three months.

[0018] The measured value in three-month age was 5.1 - 53.2 mg/dl in 4.8 -

38.0 mg/dl and a male for the female. The measured value in four-month age was 9.8 - 96.1 mg/dl in 9.0 - 94.7 mg/dl and a male for the female. Although big individual difference (variation) existed in both the measured value in age with the sex every month, high correlation was accepted between the values of three-month age and four-month age.

[0019] Therefore, the breeding by selection [/ an operation of a hereditary factor] aiming at training of a high IgA **** mouse is more strongly more possible for the individual variation in a blood serum IgA value than an environmental factor.

[0020] Furthermore, when age and the blood serum IgA value in nine-month age were measured for seven months, these values showed the value in age, and very high correlation for four months. moreover, the value in four-month age -- being based -- each sex -- when ten high orders and ten low order were extracted and aging of the blood serum IgA value in them was pursued, it became clear that the solid-state in which a high price is shown with age for four months has very remarkable lifting of the blood serum IgA value accompanying subsequent aging as compared with the solid-state in which a low value is shown. Therefore, it is appropriate to adopt the value in age for four months as an index of selection.

[0021] Then, five animals which show a high price from each sex based on the blood serum IgA value of age for four months were selected, and the next generation (the 1st generation of selection) was obtained by crossing them.

[0022] Average blood serum IgA in the 1st generation of selection When heritability (rate that heredity involves to expression) was presumed based on the ensemble genetic theory (Yokendo written by "thremmatology" Matsuo ****) by comparing the average in the ensemble who became a value and the basis of selection, and the average of a selection individual, it was 0.32 in 0.45 and a male for the female. Possibility that these values may raise a blood serum IgA value by breeding-by-selection actuation fully shows a certain thing.

[0023] Then, the selection (about 10% of high orders) which made the index the blood serum IgA value in age for ****** four months was repeated similarly hereafter.

[0024] The average of a blood serum IgA continued ****** lifting by selection, and the selection effectiveness changed into the condition of leveling off by the 4th generation of selection. Although individual difference still existed also in the 4th generation of selection, 80% or more of animal is a blood serum IgA by four-month age. A value becomes 100 or more mg/dl and came to present clear high IgA ****.

[0025] The individual variation seen in addition also after the 4th generation of selection can be said to be a nongenetic variation, judging from the

leveling-off condition of the selection effectiveness. That is, when it sees as an ensemble, it means that the system mouse with high IgA **** as a stable genetic trait was raised. Furthermore, these mice discover a remarkable kidney lesion advanced to an early stage as compared with the ensemble before selection so that it may mention later. Therefore, this invention persons succeeded in completing the first stage story of this invention of raising the system which discovers IgA glomerulonephritis Mr. symptoms, to an early stage and high rate here.

[0026] Thus, in the raised mouse, although a small number of locus had comparatively high possibility of participating in the manifestation of IgA glomerulonephritis Mr. symptoms and of being fixed to the gay, it was thought that it was difficult for many of other loci to have left heterozygosis, therefore to use this invention mouse for advanced hereditary analyses, such as investigation of a disease gene of cause, in this phase. then, ** of the animal which was continuously suitable for the hereditary analysis of an onset factor in the mouse as a second stage story of this invention, i.e., a gene presentation, -- training of an inbred strain was started that it should consider as an animal [one]. 40 generations of mating between brothers and sisters were repeated acting to ****** and a blood serum IgA value as the monitor of the glomerulosclerosis lesion. It means that all the genes (99.99% or more) that constitute genomes including the gene which participates in a symptoms manifestation by this had fixed to the theory top gay. The characteristic of discovering IgA glomerulonephritis Mr. symptoms to the early stage and high rate which were acquired on the first stage story of above-mentioned this invention is maintained at this invention mouse which completed training as an inbred strain through the sib mating of 40 generations, without changing.

[0027] The locus name in this invention is registered into the forward type in International Committee on Standardized Genetic Nomenclature for Mice (mouse international naming-convention committee). Committee For details, it can refer to by Mammalian Genome (Springer Verlag publication). About the genotype of 28 loci to Idh1-Ly1 Reference () [Genetic Variants] and Strains of the Laboratory Mouse.Ed: It determines by the approach of M.C.Green, Gustav Fischer Verlag, Stuttgart, New York, and 1981 publications. It is related with 62 loci to D1Mit43-DXMit98. By the difference in the size of the PCR product amplified by the specific primer Genotype was determined (reference: Dietrich, W.F.et al .. (1996) 380: A comprehensive genetic map of the mouse genome.Nature, 149-152.).

[0028] The gene presentation profile of this invention mouse raised as an inbred strain The genotype of Idh1 locus is an a mold and the genotype of Pep3 locus is a b mold. The genotype of Akp1 locus is a b mold and the genotype of Hc locus is an o mold. The genotype of Car2 locus is an a mold

and the genotype of Mup1 locus is an a mold. The genotype of Gpd1 locus is a b mold and the genotype of Pgm1 locus is an a mold. The genotype of Ldr1 locus is an a mold and the genotype of Gpi1 locus is an a mold. The genotype of a Hbb locus is an s mold and the genotype of Es1 locus is a b mold. The genotype of Es2 locus is a b mold and the genotype of Thy1 locus is a b mold. The genotype of Mod1 locus is an a mold and the genotype of a Trf locus is a b mold. The genotype of Es3 locus is a c mold and the genotype of H2K locus is an s mold. The genotypes of H2D locus are b mold, d mold, k mold, q mold, and a mold applicable to neither of s mold. The genotype of Ly2 locus is a b mold and the genotype of Ly3 locus is a b mold. The genotype of a Hba locus is a c mold and the genotype of an IghC locus is an a mold. The genotype of Np1 locus is an a mold and the genotype of Es10 locus is a b mold. The genotype of C3 locus is a b mold and the genotype of Glo1 locus is an a mold. The genotype of Ly1 locus is a b mold. D1Mit43 locus, D1Mit48 locus, D1Mit70 locus, D1Mit76 locus, D1Mit132 locus, D1Mit215 locus, D2Mit79 locus, D2Mit98 locus, D2Mit113 locus, D3Mit105 locus, D3Mit117 locus, D3Mit152 locus, D4Mit89 locus, D4Mit103 locus, D4Mit146 locus, D4Mit209 locus, D5Mit20 locus, D5Mit99 locus, D5Mit136 locus, D6Mit113 locus, D6Mit170 locus, D7Mit46 locus, D7Mit57 locus, D7Mit80 locus, D7Mit131 locus, D8Mit58 locus, D8Mit64 locus, D8Mit87 locus, D9Mit35 locus, D9Mit66 locus, D9Mit120 locus, D10Mit84 locus, D10Mit102 locus, D11Mit74 locus, D11Mit164 locus, D11Mit174 locus, D11Mit184 locus, D11Mit202 locus, D12Mit80 locus, D12Mit116 locus, D12Mit126 locus, D13Mit1 locus, D13Mit13 locus, D13Mit117 locus, D14Mit48 locus, D14Mit83 locus, D14Mit94 locus, D14Mit111 locus, D15Mit42 locus, D15Mit83 locus, D16Mit34 locus, D17Mit24 locus, D17Mit113 locus, D17Mit150 locus, D18Mit40 locus, The genotype of D18Mit92 locus, D19Mit6 locus, D19Mit56 locus, D19Mit61 locus, DXMit73 locus, DXMit79 locus, and DXMit98 locus differs from the genotype of a BALB/c system mouse.

[0029] Next, as a culmination of this invention, it started clarifying the onset factor in this invention mouse in gene expression analysis. Below, the gene expression analysis of this invention mouse is described.

[0030] The equalization cDNA library was produced from the kidney of a rat, and the kidney specific DNA microarray chip was produced using this. The gene expression profile in this invention mouse kidney was analyzed by making mRNA extracted from the kidney of this invention mouse react to this DNA chip. About the gene as which change in the amount of manifestations was regarded after comparing with a commercial BALB/c system mouse and a ddY system mouse, the quantum by RT-PCR method (Eds: [Molecular cloning.A Laboratory Manual.2nd ed. and] J.Sambrook, E.F.Fritsch, T.Maniatis) was performed further.

[0031] this invention mouse is set to 5-10 weeks old. The amount of 1

transforming-growth-factor beta (TGF-beta) gene expression Consequently, 1.2 to 2.0 times of a BALB/c system mouse, 2) The amount of connective tissue growth factor (CTGF) gene expression 1.2 to 5.0 times of a BALB/c system mouse, 3) The amount of collagen alpha 2(IV) chain gene expression 1.3 to 1.8 times of a ddY system mouse, 4) The amount of collagen alpha 1(IV) chain gene expression 1.3 to 1.8 times of a ddY system mouse, 5) and the amount of SAIKURIN D1 (cyclin D1) gene expression 1.5 to 4.2 times of a ddY system mouse, 6) The amount of SAIKURIN G (cyclin G) gene expression 1.5 to 2.2 times of a ddY system mouse, 7) The amount of PDGF gene expression 1.2 to 1.5 times of a ddY system mouse, 8) The amount of hepatocyte growth factor (HGF) gene expression 1.4 to 1.8 times of a ddY system mouse, 9) The amount of edg-5 gene expression 1.5 to 3.6 times of a ddY system mouse, TGF-beta and CTGF which have which property and participate in the hyperplasia of an extracellular matrix from an early stage, Growth factors, such as cyclin D1 which participates in IV mold collagen which is extracellular-matrix configuration protein, and cell proliferation and cyclin G, PDGF, and HGF, and a high manifestation clear to edg-5 were accepted.

[0032] Then, the relation of PDGF and the edg-5 gene high manifestation as which manifestation sthenia was regarded was analyzed using the culture mesangial cell separated from the rat with this invention mouse. Consequently, when the culture mesangial cell was stimulated by PDGF, it was admitted that edg-5 gene expression went up about 2.5 times the 2 hours after. It is thought that the intracellular signaling produced from this when the sphingosine-1-phosphoric acid which is the ligand and is similarly secreted from a platelet by edg-5 by which a manifestation is guided to growth of the mesangial cell in the mesangium of this invention mouse by PDGF stimulus in addition to the direct action of PDGF originating in a platelet acts is involving.

[0033] Below, system maintenance of this invention mouse is described.

[0034] this invention mouse is maintained by sib mating. The property as a high IgA **** mouse is made not to be lost by checking the blood serum IgA value of the animal used for ****** and mating. Although this invention mouse discovers high IgA ****, it is favorably maintainable by constructing mating of ****** about 5 pairs with breeding difficulties.

[0035] Below, the process of this invention mouse is described.

[0036] this invention mouse is producible by the usual approach when producing an inbred line animal. That is, the animal of a number pair is obtained from the colony which is performing system maintenance, a number required for production of seed animals are prepared by performing growth of 1-3 generations according to a production required number based on these, and these are crossed to the colony for production.

[0037] Below, the property of this invention mouse is described.
[0038] (1) A high IgA **** this invention mouse discovers high IgA **** more remarkable than the time of juvenile. The average of the blood serum IgA value in age exceeded 200 mg/dl for the sex for four months. To the ddY system mouse colony before selection, it was after nine-month age that the individual for which a blood serum IgA value exceeds 200 mg/dl appears. the average (mg/dl) of the blood serum IgA value in the ddY system mouse colony before selection -- for 27.1**2.2 and a male, the female was [the female / 76.2**6.9 and a male] 89.9**7.4 in 43.3 **3.3 or 9-month age at four-month age.
[0039] Thus, a blood serum IgA value came to show remarkable lifting from the early stage by selection mating. Moreover, simultaneously, individual difference is also reduced remarkably and 80% or more of all individuals came to discover high IgA **** of 100 or more mg/dl in age for four months.
[0040] (2) The advanced deposition of IgA to mesangium happens by 25 weeks old, and the self-possessed extent matches what becomes some conventional ddY system mice and is accepted in 40 weeks old or more in the pathology histological abnormality this invention mouse of a kidney. Growth of a mesangial cell is accepted from a 10-weeks old early stage, and the hyperplasia of a mesangium substrate advances with aging. The hyperplasia of a mesangium substrate reaches the level accepted by becoming some conventional ddY system mice by age for ten months more than 14-month age. Although these change does not differ from change seen by the conventional ddY system mouse qualitatively and remarkable acceleration is seen in the percentage of completion, the manifestation [high rate / as a new description / glomerulosclerosis lesion] which was not seen by the conventional ddY system mouse was accepted, and about 10% of glomerulus lapsed into the condition of full hardening by 40 weeks old. On the other hand, with the conventional ddY system mouse, the frequency of occurrence of the often seen demilune formation became conversely low. Thus, this invention mouse is characterized as a IgA glomerulonephritis model of a chronic hardening progress mold.
[0041] (3) In the kidney of the abnormality this invention mouse of the gene expression in a kidney, TGF-beta and CTGF gene expression sthenia it is supposed that are participated in production of extracellular-matrix protein are seen, and the high manifestation of the various matrix configuration protein genes which contain five RONEKUCHIN and IV mold collagen in connection with it is accepted. Moreover, the high manifestation of the PDGF gene it is supposed that is participated in growth of a mesangial cell, cyclin D1 which works to progress of a cell cycle, and a cyclin G gene was accepted. Furthermore, the high manifestation of edg-5 gene as which that function is not fully solved yet was accepted, being guided by PDGF began

the high manifestation of this edg-5 gene in this invention, and it was clarified.

[0042]

[Example] The example of training of this invention mouse is hung up over below, and this invention is explained in more detail.

[0043] 52 females and 52 males of the ddY system mouse currently sold as a closed colony by example Japan SLC, Inc. of training were purchased (G0 generation). The female was [27.1**2.2 and the male of the average (mg/dl) of the blood serum IgA value in the four month age of these mice] 43.3**3.3. Five animals which show a high price were selected from each sex (G0 selection individual), and the next generation (the 1st generation of selection; G1 generation) was obtained by crossing these. The female was [65.0**7.9 and the male of the average blood serum IgA value of G0 selection individual] 90.5**2.3. The female was [44.2**4.0 (n= 52) and the male of the average blood serum IgA value (four month age) in G1 generation] 58.4**6.0 (n= 55).

[0044] Next, the sex of six pairs was selected from G1 generation by having made the blood serum IgA value of age into the index for four months, and G2 generation was obtained by crossing them. The female was [109.6**12.6 and the male of the average blood serum IgA value of G1 selection individual] 147.8**15.6, and the female was [161.0**12.0 (n= 54) and the male of the G2 generation average (four-month age)] 180.4**18.1 (n= 42).

[0045] Selection mating was repeated by making the blood serum IgA value in age into an index for ****** four months similarly hereafter. The circumstances of selection to the 4th generation where the effectiveness of selection mating over blood serum IgA value lifting was reaching the ceiling were shown in a table 1.

[0046]

[A table 1]

選抜第４世代までの各世代における選抜個体およびその子孫の４ヶ月齢における血清IgA値（平均値 ± 標準誤差(個体数); mg/dl)

選抜個体			子孫		
世代	♀	♂	世代	♀	♂
			G0	27.1 ± 2.2(52)	43.3 ± 3.3(52)
G0	65.0 ± 7.9(5)	90.5 ± 2.3(5)	G1	44.2 ± 4.0(52)	58.4 ± 6.0(55)
G1	109.6 ± 12.6(6)	147.8 ± 15.6(6)	G2	161.0 ± 12.0(54)	180.4 ± 18.1(42)
G2	293.5 ± 28.2(6)	358.9 ± 50.6(6)	G3	159.4 ± 11.9(46)	222.6 ± 27.2(42)
G3	235.8 ± 25.3(5)	548.7 ±130.3(5)	G4	238.5 ± 21.0(50)	214.8 ± 20.3(39)

[0047] In the Ministry of International Trade and Industry National Institute of Bioscience and Human-Technology patent microorganism deposition pin center,large, it is entrusted with this invention mouse fertilized egg raised as

an inbred strain through the sib mating over 40 generations on December 25, Heisei 12 as trust number FERM P-18150 No.

[0048]

[Test Example(s)] The example of the pharmacometrics trial which used and carried out this invention mouse is hung up over below, and the usefulness of this invention is shown in it.

[0049] The compound 1-(1, 5-dimethyl-2-phenylindole-3-yl-carbonyl)-4-(2-pyridyl) piperazine which has TGF-beta signaling depressant action in this invention mouse female of 125 weeks old of examples of a trial Internal use of (it being hereafter called "a compound 1") and a 1-(1-methyl-2-phenylindole-3-yl-carbonyl)-4-(3-pyridyl) gay piperazine hydrochloride (henceforth "a compound 2") was continuously performed for ten weeks by the dosage of 30 mg/kg once [1] per day. The kidney was extracted at the time of repetitive administration termination, the paraffin embedding section was produced by BUAN immobilization, immunohistochemistry-dyeing using an anti-five RONEKUCHIN antibody was performed, and the rate of the five RONEKUCHIN positivity part occupied to a glomerulus field was measured using image-analysis equipment (the product name Mac SCOPE and Mitani Corp.). Measurement followed 40 glomeruli extracted from the whole sample at random using one section per one individual. The result is shown in a table 2.

[0050]

[A table 2]

※球体に占めるファイブロネクチン陽性部分の割合

被検化合物	個体数	ファイブロネクチン陽性領域(%) 平均値±標準誤差	P
コントロール(溶媒)	15	0.17 ± 0.03	
化合物1	15	0.06 ± 0.01	<0.01
化合物2	15	0.09 ± 0.02	<0.05

[0051] As shown in a table 2, it was checked that both the compound 1 with TGF-beta signaling depressant action and the compound 2 control intentionally progress of the five RONEKUCHIN deposition in the mesangium of this invention mouse by internal use.

[0052] Administration of the compound (1-(1, 5-dimethyl-2-phenylindole-3-yl-carbonyl)-4-(2-pyridyl) piperazine hydrochloride) (henceforth "a compound 3") which has TGF-beta signaling depressant action in this invention mouse female of 225 weeks old of examples of a trial was continuously performed for ten weeks in the form made to mix by the dosage of 30mg/kg/day into day 1 time per of internal use or ****. RNA was extracted from the kidney extracted at the time of

repetitive administration termination, and the quantum of the amount of CTGF gene expression was carried out by RT-PCR method. After measurement of the amount of gene expression by RT-PCR method changes into cDNA mRNA contained in a specimen, it is performed by measuring the amount of the magnification product acquired by performing a specific PCR reaction to cDNA originating in mRNA which it is going to measure. Since it depended for the amount of a magnification product on the amount of mRNA(s) contained in a specimen, mRNA of GAPDH which is one of the housekeeping gene considered that there is no difference in the amount of manifestations between individuals was adopted as an internal standard, and the amount of CTGF gene expression of an each object was computed as a ratio of the amount of a CTGF magnification product to the amount of a GAPDH magnification product. The result is shown in a table 3.

[0053]

[A table 3]

CTGF 遺伝子発現量の GAPDH 遺伝子発現量に対する比

マウス系統(処置)	個体数	CTGF mRNA ／ GAPDH mRNA
ddY(無処置)	5	0.039 ± 0.001
本発明マウス(無処置)	15	0.058 ± 0.002
本発明マウス(化合物3 経口)	15	0.034 ± 0.002**
本発明マウス(化合物3 混餌)	15	0.031 ± 0.003**

＊＊：本発明マウス（無処置）との比較で有意差あり（$p<0.01$）

[0054] As shown in a table 3, it was checked that the compound 3 with TGF-beta signaling depressant action controls the CTGF gene expression which is accelerating with this invention mouse even on normal level by administration as taking orally or a mixed feed.

[0055]

[Effect of the Invention] This invention mouse The time course which results in a symptoms manifestation unlike the ddY system mouse known as an only model animal which carries out the natural onset of the IgA glomerulonephritis Mr. symptoms is very short, and since an advanced lesion is seen by high rate (80% or more), the effectiveness and economical effectiveness of using this invention mouse as a drug effect valuation modeling are very large. Moreover, since the factor which participates in the onset is clarified with the molecular level, this invention mouse is very useful although the screening system of the new molecular entity which used these molecules as the target is built using the organization of this invention mouse origin, and the cell of this invention mouse origin.

[Translation done.]